Hormone Replacement Therapy in Type 2 Diabetes Mellitus: a Cardiovascular Perspective

Until recently, a diagnosis of diabetes was considered a relative contraindication for hormone replacement therapy (HRT) in post-menopausal women. This is reflected by an uptake of HRT of only around 10 % (approximately half that in the non-diabetic population).[1,2] However, a recent series of reviews on the subject postulated that, due to their increased risk of vascular disease, post-menopausal women with Type 2 diabetes (Type 2 DM) may derive particular benefit from HRT.[3–5] These reviews, extrapolating from results of studies in non-diabetic women, suggested potential improvements in several biochemical pathways relating to atherogenesis in diabetes: insulin resistance and glycaemic control, lipid and lipoprotein concentrations, oxidative stress, and prothrombotic changes. Recently published studies have provided some much needed insights into potential benefits of HRT for post-menopausal women with Type 2 DM.

Turning first to insulin resistance and glycaemic control, two randomized placebo controlled trials[6,7] have provided promising results. Andersson *et al.*[6] treated 25 women with Type 2 DM with 2 mg 17-β-oestradiol for 3 months in a double-blind, crossover fashion. As well as conventional exclusion criteria (e.g thromboembolic disease), patients on insulin therapy were omitted from the study. They observed significant reductions of around 20 % in fasting glucose and 14 % reduction in HbA_{1c} in the oestradiol treated group. C-peptide concentrations also fell by around 16 %, and there was a trend for an increase in whole body glucose disposal. Unfortunately, hepatic glucose production was not assessed in this study. Brussard *et al.*[7] also examined the metabolic effects of 2 mg 17-β-oestradiol in a similar group of patients for a shorter period (6 weeks), but employed a more straightforward double-blind design, and in addition excluded patients on metformin therapy. Nevertheless, the results were consistent, demonstrating a smaller (3.5 %) but significant reduction in HbA_{1c}. There was no effect of oestrogen replacement on whole body glucose disposal but suppression of hepatic glucose production by insulin was significantly enhanced, particularly in those patients with triglyceride levels less than 2.0 mmol l^{-1} at baseline. In both studies weight increased slightly but significantly with oestradiol treatment, suggesting the improvements in glucose metabolism were unrelated to changes in BMI.

These two studies strongly suggest that unopposed oral oestradiol improves glycaemic control in patients with diabetes. Furthermore, the predominant mechanism for this improvement appears to be an enhancing effect of oestradiol on insulin sensitivity at the liver, rather than peripherally. This would suggest that oral HRT preparations are likely to offer more pronounced effects with respect to glycaemic control than transdermal preparations. Consistent with this possibility, Mosnier-Pudar *et al.*[8] observed no change in plasma HbA_{1c} or fructosamine after 6 months of transdermal oestradiol therapy in women with diabetes. In contrast to 'natural' oestrogen, information on the metabolic effects of conjugated oestrogens in diabetic subjects is currently lacking, but it is significant that in non-diabetic subjects some deterioration of glucose tolerance and increased plasma insulin concentrations have been seen in those receiving oral HRT containing conjugated equine oestrogen with or without progestogen.[9]

With respect to lipids and lipoprotein levels, results from the ARIC study suggested that women with Type 2 DM have a blunted response to the HDL-raising effects of oestrogen (6 % rise vs 16 % in control subjects), and an exaggerated hypertriglyceridaemic response (25 % vs 16 %).[1] Differences in LDL-cholesterol, apo AI and apo B between hormone users and non-users in diabetic and non-diabetic women were similar. However, these results were based upon cross-sectional analyses and unknown selection factors may have influenced the use of hormone replacement in some women. There was no information on formulations (conjugated oestrogens vs natural oestradiol) and doses used. The lipid results from randomized trials of unopposed oestradiol, however, have been more encouraging. These have suggested that HDL-cholesterol increases by around 20 % in diabetic women treated with oral oestradiol,[6,7] a figure comparable to data from studies in non-diabetic women. Furthermore, this rise in HDL was predominantly in the cardioprotective HDL2 subfraction and, as LDL-cholesterol was reduced by 15–24 %, the LDL:HDL ratio declined by around one-third. Importantly, triglyceride concentrations increased only marginally and non-significantly in both studies (3–12 %), alleviating concerns arising from the ARIC study of an exaggerated rise in this parameter in diabetic women. Indeed, if anything the changes in triglyceride concentrations were slightly less than those seen previously in studies in non-diabetic subjects[10] and may reflect an oestradiol-mediated enhanced suppression of hepatic triglyceride synthesis by insulin, i.e. improved insulin sensitivity similar to the effects on glucose

*Correspondence to: Dr Naveed Sattar, Department of Pathological Biochemistry, Macewen Building, Royal Infirmary, Glasgow G4 0SF, UK. E-mail: nsattar@clinmed.gla.ac.uk

CCC 0742–3071/98/080631–03$17.50

metabolism. In line with the lack of change in triglyceride concentrations, Brussard *et al*. observed no significant change in LDL particle size, but in contrast to expectations, oestradiol replacement also had no appreciable effect on LDL oxidizability.[11] There is currently no information on the effects of HRT in diabetic women on circulating lipid peroxide and antioxidant concentrations, but clearly future studies should also examine for changes in these parameters.

Thus with respect to lipids, the overall effects of oral oestradiol therapy are extremely favourable and consistent with the pattern observed in non-diabetic subjects. Furthermore, since the majority of lipid effects of oestradiol are likely to be mediated at the liver (LDL receptor up-regulation with resultant increased catabolism, increased HDL apo AI synthesis, and decreased hepatic lipase activity—which is higher in diabetic patients—with resultant decreased HDL catabolism),[3] then with respect to lipid levels oral therapies are also more likely to demonstrate more pronounced effects than transdermal preparations. Also consistent with this suggestion, a previous study of a combination of transdermal oestradiol and natural progesterone in women with Type 2 DM, observed no change in plasma levels of cholesterol, HDL-cholesterol, triglycerides, and apolipoproteins A1 and B.[8]

As part of the insulin resistance syndrome, patients with diabetes exhibit elevated levels of the fibrinolytic inhibitor plasminogen activator inhibitor-1 (PAI-1), leading to a prothrombotic state. It is, therefore, significant that oral oestradiol has been shown to reduce PAI-1 activity by around 50 %, explained in part by a reduction in PAI-1 antigen levels[7] and accompanied by a small increase in tissue plasminogen activator (tPA) activity. Overall these changes would suggest a significant reduction in thrombotic tendency with oral oestradiol therapy in diabetic subjects. Clearly, information on the response to HRT of other haemostatic factors is needed.

An alternative to oestrogen or combined oestrogen and progestogen HRT is tibolone. This is a synthetic steroid possessing weak oestrogenic, progestogenic and androgenic properties. Feher *et al*.[12] studied the metabolic effects of an 8-week course of tibolone in 10 women with Type 2 DM. This study was not placebo controlled. The results were less impressive than those seen with oestradiol: triglyceride and lipoprotein(a) concentrations declined significantly (presumably as a result of androgenic effects at the liver), but there was no change in LDL-cholesterol; and HDL-cholesterol declined, resulting in an increase in the LDL:HDL ratio of 26 %. In addition, no beneficial effect was observed on glycaemic control.

To date, results obtained with unopposed oral oestradiol therapy in women with Type 2 DM are promising, with beneficial effects on glycaemic control, lipids and lipoprotein levels, and thrombotic indices. However, trials that are larger and for longer periods are needed before HRT can be recommended unconditionally. More importantly, as the majority of women are unsuitable for unopposed oestrogen therapy, trials looking at the effects of combined oestrogen and progestogen preparations in women with Type 2 DM are needed. From existing literature in non-diabetic subjects, we may anticipate a partial reduction of the oestradiol mediated improvements in glycaemic control, but the extent of this and the relative effects of differing progestogenic agents need to clarified.

With respect to lipids, the addition of a progestogen is unlikely to effect the oestradiol mediated change in LDL-cholesterol, but it is likely to lessen the rise in HDL-cholesterol. On the plus side, triglyceride concentrations generally decrease with progestogens so any tendency for this parameter to increase with oral oestradiol therapy may be completely negated or reversed.[13] It is noteworthy, however, that in the recently published Nurses Health Study,[14] the beneficial effects with respect to cardiovascular disease in non-diabetic women were greatest among those who used combined HRT when compared with women who took oestrogen alone or did not use HRT. Thus, the addition of a progestogen which was predicted to negate some of the cardiovascular protection of oestrogen, did not appear to do so. Whether combined oestrogen and progestogen HRT will have similar effects in women with diabetes is the subject of ongoing research.

Finally, since resumption of monthly bleeding is a major reason for poor long-term compliance with cyclical HRT therapies, use of continuous combined HRT preparations is likely to be favoured. With these preparations, the progestogen can be given orally, or via an intrauterine system, can be released directly into the uterus. This latter option has the potential advantage of escaping systemic effects of the progestogen while retaining the metabolic benefits of oral oestradiol treatment.

In summary, current evidence suggests that postmenopausal women with Type 2 DM considering HRT should be recommended oral preparations containing oestradiol. If combined HRT is required, the ideal choice of progestogen(s) remains to be established.

Acknowledgements

We are indebted to the Jeffrey Charitable Trust for their current support of our work in this field.

N. Sattar*[1], J. McKenzie[2], A.C. MacCuish[2], A.J. Jaap[2]
[1]*Department of Pathological Biochemistry, Royal Infirmary University NHS Trust, Glasgow, UK*
[2]*Department of Diabetes, Royal Infirmary University NHS Trust, Glasgow, UK*

References

1. Robinson JG, Folsom AR, Nabulsi AA, Watson R, Brancati FL, Cai Jiawen for the Atherosclerosis Risk In Community Study Investigators. Can postmenopausal hormone

replacement improve plasma lipids in women with diabetes? *Diabetes Care* 1996; **19**: 480–485.
2. Feher MD, Isaacs AJ. Is hormone replacement therapy prescribed for postmenopausal diabetic women? *Br J Clin Pract* 1996; **50**: 431–432.
3. Sattar N, Jaap AJ, MacCuish AC. HRT and cardiovascular disease in women with NIDDM. *Diabetic Med* 1996; **13**: 782–788.
4. Dunne FP, Keane HL, Jenkins D, Wright AD. Hormone replacement therapy and diabetes mellitus. *Clin Endocrinol* 1996; **44**: 615–620.
5. Westerveld HE. Hormone replacement therapy for diabetic women. *Diabetes Reviews International* 1996; **5**: 1–2.
6. Andersson B, Mattsson L, Hahn L, Marin P, Lapidus L, Holm G, *et al*. Oestrogen replacement therapy decreases hyperandrogenicity and improves glucose homeostasis and plasma lipids in post-menopausal women with noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1997; **82**: 638–643.
7. Brussard HE, Gevers Leuven JA, Frolich M, Kluft C, Krans HMJ. Short-term oestrogen replacement therapy improves insulin resistance, lipids, and fibrinolysis in postmenopausal women with NIDDM. *Diabetologia* 1997; **40**: 843–849.
8. Mosnier-Pudar H, Faguer B, Guyenne TT, Tchobroutsky G. Effects of deprivation and replacement by percutaneous 17 beta oestradiol and oral progesterone on blood pressure and metabolic parameters in menopause patients with non-insulin-dependent diabetes. *Archives des Maladies du Coeur et des Vaisseaux* 1991; **84**: 1111–1115.
9. Stevenson JC, Crook D, Godsland IF, Collins P, Whitehead MI. Hormone replacement therapy and the cardiovascular system: non-lipid effects. *Drugs* 1994; **47** (suppl. 2): 35–41.
10. Walsh BW, Schiff I, Rosner B, Greenberg L, Ravnikar V, Sacks FM. Effects of postmenopausal oestrogen replacement on the concentrations and metabolism of plasma lipoproteins. *N Engl J Med* 1991; **325**: 1196–1204.
11. Brussard HE, Gevers Leuven JA, Kluft C, Krans HMJ, van Duyenvoorde W, Butenhek R, *et al*. Effect of 17β-estradiol on plasma lipids and LDL oxidation in post-menopausal women with type II diabetes mellitus. *Arterioscler Thromb Vasc Biol* 1997; **17**: 324–330.
12. Feher MD, Cox A, Levy A, Mayne P, Lant AF. Short term blood pressure and metabolic effects of tibolone in postmenopausal women with non-insulin dependent diabetes. *Brit J Obstet Gynaecol* 1996; **103**: 281–283.
13. Sattar N, Jaap A. Hormone replacement preparations and hypertriglyceridaemia in women with NIDDM (Letter). *Diabetes Care* 1997; **20**: 234–235.
14. Grodstein F, Stampfer MJ, Manson JE. Postmenopausal oestrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996; **15**: 453–461.

